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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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HELLER EHRMAN WHITE & MCAULIFFE LLP 275 MIDDLEFIELD ROAD MENLO PARK, CA 94025-3506			EPPERSON, JON D	
			ART UNIT	PAPER NUMBER
			1639	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary**Application No.**

09/990,421

Applicant(s)

ERLANSON ET AL.

Examiner

Jon D Epperson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 February 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-74 is/are pending in the application.
- 4a) Of the above claim(s) 7,26-32,44-49,60-63 and 68-74 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6 and 8-19 is/are rejected.
- 7) ☒ Claim(s) 20-25,33-43,50-59 and 64-67 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>7/21, 7/16, 2/11</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the Application

1. Receipt is acknowledged of a Response to a Restriction Requirement, which was dated on February 11, 2004.

Status of the Claims

2. Claims 1-74 are pending.
3. Applicant's response to the Restriction and/or Election of Species requirements in the 2/11/2004 Response is acknowledged (Applicant elected with traverse Group I, claims 1-43 and 50-68) and claims 44-49 and 69-74 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim (see *Response to Restriction and/or Election of Species* below).
4. Please note: Applicant's elected species (Subgroups 2 and 8 = disulfide library, Subgroups 4 and 9 = dithiothreitol; Subgroup 5 = thiol; Subgroup 10 = mass spectrometry; Subgroup 11 = fluorescent label) was found in the art. Furthermore, Applicant's *specifically* elected species (Subgroup 1 = capase 3; Subgroup 3 = 2,6-dichloro-benzoic acid 3-(2-acetylsulfanyl-acetylamino)-4-carboxy-2-oxo-butyl ester; Subgroup 6 = Michael-type adduct with thiol; Subgroup 7= α -halo acid; Subgroup 12 = compound in figure 5) was searched and

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was not found in the prior art. Thus, the search was expanded to non-elected species, which *were* found in the prior art, see rejections below. Also, see MPEP § 803.02 (emphasis added):

On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. *The prior art search, however, will not be extended unnecessarily to cover all nonelected species.* Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

5. Claims 7, 26-32, 60-63 and 68 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species (see *Response to Restriction and/or Election of Species* below).

6. Therefore, claims 1-6, 8-25, 33-43, 50-59 and 64-67 are examined on the merits in this action.

Response to Restriction and/or Election of Species

7. Applicant's election of Group I (i.e., claims 1-43 and 50-68) **with traverse** in the 2/11/2004 Response is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a) and/ or 37 CFR 1.111(b)).

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8. Applicant's election of species in the 2/11/2004 Response is also acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has also been treated as an election without traverse (MPEP § 818.03(a) and/ or 37 CFR 1.111(b)).

9. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

10. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on the form PTO-892, they have not been considered.

11. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action.

Specification

12. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. **Claims 1 and 50** recite “near” a site of interest. The term “near” is a relative term, which renders the claim indefinite and/or unclear. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. See also MPEP § 2173.05(b).

B. **Claim 1** recites the limitation “the first ligand” in step (iii). There is insufficient antecedent basis for this limitation in the claim.

C. **Claim 2, 14** recite the limitation “said ligand candidates.” There is insufficient antecedent basis for this limitation in the claim. In addition, it is not clear whether the ligand candidates refer to the “first” or the “second” ligands. Clarification is requested.

D. **Claims 9-13** recite the limitation “said nucleophile.” There is insufficient antecedent basis for this limitation in the claim.

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E. *Claim 50* recites the limitation "the first ligand" in step (iii). There is insufficient antecedent basis for this limitation in the claim.

F. *Claim 50* recites the limitation "the conditions" in step (iii). There is insufficient antecedent basis for this limitation in the claim.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-6 and 9-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim et al. (WO 98/11436) (Date of Patent is **19 March 1998**) (Paper No. 5, IDS Reference 14).

For *claims 1*, Kim et al. (see entire document) disclose non-specific affinity enhancement methods for identifying combinatorial library members (see Kim et al., abstract), which anticipate claim 1. For example, Kim et al. disclose (i) a target biological molecule (TBM) having a first and a second site of interest (e.g., see figure 2, wherein the Target Biological Molecule (referred to herein as TBM) is the "target protein-cell membrane-anchor/FKBP" complex (referred to herein as TP-FKBP) and the first and second sites of interest are the target protein (TP) and FKBP receptor, respectively). Kim et al. also disclose contacting said TP-FKBP with a plurality of first

small organic ligand candidates (e.g., see figure 2, wherein the ligand candidates are labeled as “combichem moiety”; see also page 15, lines 17-25, “For example, as shown in Figure 2, the library can be comprised of potential ligands joined to FK-506 by means of a linker. Recognition and binding of FK-506 with the FKBP on the cell membrane tethers the potential ligand with the target molecule, increasing the effective concentration relative to one another and enhancing the likelihood they will bind and a ligand will be identified”; see also page 21, lines 15-20, wherein the library ligands are identified as “small organic molecules, pharmaceuticals, toxins”; see also claim 3 further disclosing “steroids, hormones, caffeine, ATP, cyclosporin, cyclophilin”). In addition, Kim et al. conditions such that a reversible covalent bond is formed between the library of ligands and the TBM to form a TBM-first ligand complex including covalent binding via disulfide exchange (e.g., see claims 1-2, “target molecule, as obtained or as modified, contains one member of a binding pair ... wherein the binding partner and the reactive moiety are each a free sulfhydryl group [i.e., an –SH group] or a sulfur moiety which is available for disulfide bond formation through exchange”; see also page 3, paragraphs 2-3; see also page 11, paragraph 2, “As obtained, a target molecule might also include a binding partner (such as a sulfur moiety within a cysteine residue) which is available or can be made available (e.g., as a free sulfhydryl group or sulfur that is available for disulfide bond formation through exchange) for binding with a reactive moiety. If such a target molecule is used potential ligands [i.e., at least 2] can be modified to include a free sulfhydryl group or a sulfur that is available for disulfide bond formation through exchange ... Here, non-specific binding of target molecule and potential ligands occurs

through formation of a disulfide bond”; see also page 17, paragraph 1 disclosing the use of reducing agents, “non-specific interaction (here, disulfide bond formation) can be varied by adjusting the concentration of external ... reducing agents ... for example ... glutathione”).

Kim et al. also disclose **(ii)** determining the “identity” of the non-oligomeric ligand present in said target protein-ligand conjugate (e.g., see Kim et al, abstract, “Non-specific affinity enhancement as a method of identifying and detecting members, such as ligands ... in a collection or library of potential ligands”; see also Summary of the Invention; see also page 8, lines 18-20). In addition, Kim et al. disclose **(iii)** “designing derivatives of the first ligand” that possess small molecule extender (SME) and first and second functional groups that react with the TBM and second site of interest, respectively (e.g., see figure 2 wherein SME is the “linker” and the first and second sites of interest are the “combichem moiety” and “FK-506,” respectively; see also page 14, paragraph 1, especially lines 12-18, “If further ligands are desired (e.g., with greater binding affinity) [i.e., derivatives], knowledge of the characteristics of the ligand can be used to design a biased library of potential ligands (e.g., a library of potential ligands in which a region of the ligand identified which appears to be critical for binding varied based on characterization of the ligand identified)”; see also paragraph bridging pages 14-15).

For *claim 2*, Kim et al. disclose sequential contacts (e.g., see page 13, lines 26-29, “These interactions may occur individually (e.g., only one type of interaction occurs), sequentially (e.g., one type of interaction occurs, followed by the second type) or simultaneously”).

For *claim 3*, Kim et al. disclose members of a library (e.g., see page 15, lines 17-25, “For example, as shown in Figure 2, the library can be comprised of potential ligands joined to FK-506 by means of a linker”).

For *claims 4-5*, Kim et al. disclose polypeptides and proteins (e.g., see page 4, lines 20-31).

For *claim 6*, Kim et al. disclose, for example, hormones (e.g., see page 20, line 19).

For *claims 9-14 and 18*, Kim et al. disclose, for example, a thiol that forms a reversible disulfide (e.g., see claims 1-2, “target molecule, as obtained or as modified, contains one member of a binding pair ... wherein the binding partner and the reactive moiety are each a free sulfhydryl group [i.e., a thiol] or a sulfur moiety which is available for disulfide bond formation through exchange”; see also page 3, paragraphs 2-3; see also page 11, paragraph 2). Kim et al. disclose, for example, Cys (e.g., see page 11, paragraph 2, “As obtained, a target molecule might also include a binding partner (such as a sulfur moiety within a cysteine residue) which is available or can be made available (e.g., as a free sulfhydryl group or sulfur that is available for disulfide bond formation through exchange) for binding with a reactive moiety”).

For *claim 15*, Kim et al. disclose Furthermore, Kim et al disclose the formation of a target protein-ligand conjugate under thiol exchange conditions (e.g., see Kim et al, claims 1-2; see also page 3, paragraphs 2-3; see also page 9, line 14; see also page 14, paragraph 1; see also page 28, paragraph 1, “This experiment illustrates under conditions wherein a specific interaction between a target molecule and ligand can take place,

preferential formation of disulfide-mediated ligand-target heterodimers [i.e., a target protein-ligand conjugate] can be observed”).

For **claim 16**, Kim et al. disclose, for example, glutathione (e.g., see page 17, lines 15 and 25; see also page 26, line 30; see also page 28, line 9).

For **claim 17**, Kim et al. disclose, for example, the formation of a covalent linkage (e.g., see page 12, lines 10-12, “the ligand is modified by the addition of a covalent, flexible linker and a reactive moiety, in such a manner that the linker positioned between the ligand and the reactive moiety”).

For **claims 50**, Kim et al. disclose (i) a target biological molecule (TBM) having a nucleophile near a site of interest (e.g., see figure 1 where -SH group is disclosed near ligand binding site of TBM; see also figure 2; see also page 3, line 13; see also page 5, first full paragraph; see especially page 11, first full paragraph). Kim et al. also disclose (ii-iii) contacting the TBM with a small molecule extender having a group reactive with the nucleophile on the TBM and having a free thiol or protected thiol and adjusting the conditions to cause a covalent bond to be formed between the nucleophile on the TBM and the group on the small molecule extender (e.g., see page 11, first full paragraph; see also page 16, first full paragraph wherein the SME is the “linker” disclosed therein; see also page 16, last paragraph; see especially page 26, line 7; see also page 26, line 27; see also page 27, line 19). Kim et al. also disclose

Kim et al. also disclose contacting said TP-FKBP with a plurality of first small organic ligand candidates (e.g., see figure 2, wherein the ligand candidates are labeled as “combichem moiety”; see also page 15, lines 17-25, “For example, as shown in Figure 2,

the library can be comprised of potential ligands joined to FK-506 by means of a linker. Recognition and binding of FK-506 with the FKBP on the cell membrane tethers the potential ligand with the target molecule, increasing the effective concentration relative to one another and enhancing the likelihood they will bind and a ligand will be identified”; see also page 21, lines 15-20, wherein the library ligands are identified as “small organic molecules, pharmaceuticals, toxins”; see also claim 3 further disclosing “steroids, hormones, caffeine, ATP, cyclosporin, cyclophilin”). In addition, Kim et al. conditions such that a reversible covalent bond is formed between the library of ligands and the TBM to form a TBM-first ligand complex including covalent binding via disulfide exchange (e.g., see claims 1-2, “target molecule, as obtained or as modified, contains one member of a binding pair ... wherein the binding partner and the reactive moiety are each a free sulfhydryl group [i.e., an –SH group] or a sulfur moiety which is available for disulfide bond formation through exchange”; see also page 3, paragraphs 2-3; see also page 11, paragraph 2, “As obtained, a target molecule might also include a binding partner (such as a sulfur moiety within a cysteine residue) which is available or can be made available (e.g., as a free sulfhydryl group or sulfur that is available for disulfide bond formation through exchange) for binding with a reactive moiety. If such a target molecule is used potential ligands [i.e., at least 2] can be modified to include a free sulfhydryl group or a sulfur that is available for disulfide bond formation through exchange ... Here, non-specific binding of target molecule and potential ligands occurs through formation of a disulfide bond”; see also page 17, paragraph 1 disclosing the use of reducing agents, “non-specific interaction (here, disulfide bond formation) can be

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varied by adjusting the concentration of external ... reducing agents ... for example ... glutathione”).

Kim et al. also disclose (ii) determining the “identity” of the non-oligomeric ligand present in said target protein-ligand conjugate (e.g., see Kim et al, abstract, “Non-specific affinity enhancement as a method of identifying and detecting members, such as ligands ... in a collection or library of potential ligands”; see also Summary of the Invention; see also page 8, lines 18-20). In addition, Kim et al. disclose (iii) “designing derivatives of the first ligand” that possess small molecule extender (SME) and first and second functional groups that react with the TBM and second site of interest, respectively (e.g., see figure 2 wherein SME is the “linker” and the first and second sites of interest are the “combichem moiety” and “FK-506,” respectively; see also page 14, paragraph 1, especially lines 12-18, “If further ligands are desired (e.g., with greater binding affinity) [i.e., derivatives], knowledge of the characteristics of the ligand can be used to design a biased library of potential ligands (e.g., a library of potential ligands in which a region of the ligand identified which appears to be critical for binding varied based on characterization of the ligand identified)”; see also paragraph bridging pages 14-15).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1-6, 8-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erlanson et al. (Erlanson, D. A.; Braisted, A. C.; Raphael, D. R.; Randal, M.; Stroud, R. M.; Gordon, E. M.; Wells, J. A. "Site-directed ligand Discovery" *PNAS* **August 15, 2000**, 97(17), 9367-9372) (Paper No. 5, IDS Reference 29) and Hajduk et al. (Hajduk, P. J.; Sheppard, G.; Nettesheim, D. G.; Olejniczak, E. T.; Shuker, S. B.; Meadows, R. P.; Steinman, D. H.; Carrera, G. M.; Marcotte, P. A.; Severin, J.; Walter, K.; Smith, H.; Gubbins, E.; Simmer, R.; Holzman, T. F.; Morgan, D. W.; Davidsen, S. K.; Summers, J. B.; Fesik, S. W. "Discovery of Potent Nonpeptide Inhibitors of Stromelysin Using SAR by NMR" *J. Am. Chem. Soc.* **1997**, 119, 5818-5827).

For *claim 1*, Erlanson et al. (see entire document) teach site directed ligand discovery (e.g., see abstract), which reads on claim 1. For example, Erlanson et al. teach (i) a Target Biological Molecule (TBM) having a first and a second site of interest (e.g., see Erlanson et al., figure 1A showing open "circle" and "square" as the first and second

sites of interest, respectively; see also figures 2,4 and Materials and Methods section).

Erlanson et al. also teach a TBM that contains or has been modified to contain a nucleophile at or near the first site of interest (e.g., see Erlanson et al., figure 1A showing an -SH group at the site of interest; see also Materials and Methods section). In addition, Erlanson et al. also teach contacting the TBM with a plurality of first small organic ligand candidates (e.g., see compounds listed in figure 3; see also Materials and Methods section; see also figure 2). Erlanson et al. also teach using conditions that allow a reversible covalent bond between the nucleophile and a candidate that has affinity for the first site of interest to form a TBM-first ligand complex including 2-mercapotoethanol (e.g., see Erlanson et al., Figure 1A legend; see also Materials and Methods, Disulfide library screening section; see also Figure 2). In addition, Erlanson et al. teach (ii) identifying the first ligand use techniques like mass spectrometry (e.g., see figure 2; see also page 9370, column 2, last paragraph; see also Material and Methods; see also page 9371, column 2, last paragraph).

For *claim 3*, Erlanson et al. disclose a disulfide library (e.g., see Materials and Methods section).

For *claims 4-6*, Erlanson et al. disclose, for example, thymidylate synthase enzyme (e.g., see abstract; see also Materials and Methods section).

For *claims 9-14*, Erlanson et al. disclose a cysteine thiol nucleophile that can form reversible a reversible disulfide bond (e.g., see Erlanson et al., abstract).

For *claim 15-16*, Erlanson et al. disclose thiol exchange conditions including the use of 2-mercaptoethanol (e.g., see abstract; see also figure 1 legend; see also Materials and Methods, Disulfide library screening section).

The prior art teachings of Erlanson et al. differ from the claimed invention as follows:

For *claims 1, 17-19*, the Erlanson et al. reference is deficient in that it does not specifically teach the use of designing a derivative of the first ligand identified in (ii) to provide a small molecule extender (SME) having a first functional group reactive the nucleophile on the TBM and a second functional group reactive with a second ligand having affinity for the second site of interest.

For *claim 8*, the Erlanson et al. reference is deficient in that it does not teach the specific proteins listed in claim 8.

However, Hajduk et al. teach the following limitations that are deficient in Erlanson et al.:

For *claim 1*, Hajduk et al. (see entire document) teach designing a derivative of the first ligand identified in (ii) to provide a small molecule extender (SME) having a first functional group reactive with the nucleophile on the TBM and a second functional group reactive with a second ligand having affinity for the second site of interest (see Hajduk et al., figure 2; see also Conclusion, especially page 5822, column 2, last paragraph, "As summarized in Figure 2, the inhibitors were discovered by tethering two ligands that bind weakly to the protein, guided by structural information [i.e., information obtained from

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Erlanson et al. technique] on how they bind" wherein the "linker" that tethers the two ligands represents the SME).

For *claim 8*, Hajduk et al. disclose proteases like stromelysin (e.g., see Hajduk et al., page 5818, column 2, last paragraph).

For *claims 17-19*, Hajduk et al. disclose the use of a covalent methylene linker as an SME (e.g., see page 5821, column 1, Design and Synthesis of Linked Compounds section, especially second full paragraph, "Since compounds containing capped hydroxyl groups (e.g., 10) exhibited no loss in binding affinity to stromelysin, an ether linkage connecting the phenolic OH of the biphenyl to the hydroxamic acid was incorporated into the design ... To allow for uncertainties in the ligand position, methylene linkers of varying length were incorporated into the linked compounds"; see also Table 4; see also figure 2; see also Materials and Methods section).

It would have been obvious to one skilled in the art at the time the invention was made to extend the tethering technology disclosed by Erlanson et al. with the "SAR by NMR" strategy disclosed by Hajduk et al. to link more than one ligand together because Erlanson et al. explicitly state that this would be an obvious variant of their work and explicitly reference the Hajduk et al. reference in support of this position (e.g., see Erlanson et al., page 9371, column 2, middle paragraph, "A reasonable [i.e., obvious] extension of the tethering technology would be to discover two weakly binding fragments that bind near one another and to link them [i.e., using an SME] to produce higher affinity compounds ... In many cases, the new linked compounds bind to the target protein with much higher affinity than the precursors (33)"; please note reference (33) is

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the Hajduk et al. reference used in this rejection). Furthermore, one of ordinary skill in the art would have been motivated to use the "SAR by NMR" approach as taught by Hajduk et al. to link the ligands discovered by the tethering approach of Erlanson et al. because Erlanson et al. explicitly states that "the newly linked compounds bind to the target protein with much higher affinity than the precursors ... [and that] our [i.e., Erlanson et al.] approach can also rapidly generate candidate molecules for linking [i.e., the Hajduk et al. approach]" (see Erlanson et al., page 9371, column 2, middle paragraph). Finally, one of ordinary skill in the art would have reasonably expected to be successful because Erlanson et al. explicitly state that their tethering approach "can" also rapidly generate candidate molecules for the linking approach disclosed by Hajduk et al. (see Erlanson et al., page 9371, column 2, middle paragraph).

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

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19. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 1-6, 8-25, 33-43, 50-59 and 64-67 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent Application Publication 2003/0104471 A1 (see especially claims 32-39 of '471). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the referenced patent are drawn essentially to same method of screening a library and, as a result, the inventions overlap in scope. For example, both references claim [a] method steps for "identifying" a library of small organic compounds that bind to a Target Biological Molecule (TBM) (e.g., compare claim 32 of '471 to claim 1 step (ii) of the present application), [b] using a Target Biological Molecule that has a first and second site of interest (e.g., compare claims 35-36 of '471 to claim 1 of the present application), [c] wherein the TBM contains or is modified to contain a nucleophile at or near the first site of interest such that said candidates having a functional group reactive with the nucleophile are placed under conditions that allow a reversible covalent bond to be formed between the nucleophile and said candidate (e.g., compare claims 15, 24, 25 of '471 to claims 1 and 12 of the present application wherein the reversible covalent disulfide bond is disclosed), and [d] designing a derivative of the first ligand

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identified in (ii) to provide a small molecule extender (SME) having a first functional group reactive with the nucleophile on the TBM and a second functional group reactive with a second ligand having affinity for the second site of interest (e.g., compare claim 32 step (c) to claim 1 step (iii)). Accordingly it is deemed that the inventions claimed herein and that of the patent are obvious variants of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

21. Claims 1-6, 8-25, 33-43, 50-59 and 64-67 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent Application Publication 2002/0081621 A1 (see especially claims 32-39 of '621). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the referenced patent are drawn essentially to same method of screening a library and, as a result, the inventions overlap in scope. For example, both references claim [a] method steps for "identifying" a library of small organic compounds that bind to a Target Biological Molecule (TBM) (e.g., compare claim 32 of '621 to claim 1 step (ii) of the present application), [b] using a Target Biological Molecule that has a first and second site of interest (e.g., compare claims 35-36 of '621 to claim 1 of the present application), [c] wherein the TBM contains or is modified to contain a nucleophile at or near the first site of interest such that said candidates having a functional group reactive with the nucleophile are placed under conditions that allow a reversible covalent bond to be formed between the nucleophile and said candidate (e.g., compare claims 15, 24, 25 of '621 to claims 1 and 12 of the present application wherein the

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reversible covalent disulfide bond is disclosed), and [d] designing a derivative of the first ligand identified in (ii) to provide a small molecule extender (SME) having a first functional group reactive with the nucleophile on the TBM and a second functional group reactive with a second ligand having affinity for the second site of interest (e.g., compare claim 32 step (c) to claim 1 step (iii)). Accordingly it is deemed that the inventions claimed herein and that of the patent are obvious variants of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. Claims 1-6, 8-25, 33-43, 50-59 and 64-67 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent Application Publication 2002/0022233 A1 (see especially claims 32-39 of '233).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the referenced patent are drawn essentially to same method of screening a library and, as a result, the inventions overlap in scope. For example, both references claim [a] method steps for "identifying" a library of small organic compounds that bind to a Target Biological Molecule (TBM) (e.g., compare claim 32 of '233 to claim 1 step (ii) of the present application), [b] using a Target Biological Molecule that has a first and second site of interest (e.g., compare claims 35-36 of '233 to claim 1 of the present application), [c] wherein the TBM contains or is modified to contain a nucleophile at or near the first site of interest such that said candidates having a functional group reactive with the nucleophile are placed under conditions that allow a reversible covalent bond to be formed between the nucleophile and said candidate

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(e.g., compare claims 15, 24, 25 of '233 to claims 1 and 12 of the present application wherein the reversible covalent disulfide bond is disclosed), and [d] designing a derivative of the first ligand identified in (ii) to provide a small molecule extender (SME) having a first functional group reactive with the nucleophile on the TBM and a second functional group reactive with a second ligand having affinity for the second site of interest (e.g., compare claim 32 step (c) to claim 1 step (iii)). Accordingly it is deemed that the inventions claimed herein and that of the patent are obvious variants of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject matter

23. No claims are allowed. However, claims 20-25, 33-43, 50-59 and 64-67 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, AND/OR if rewritten in independent form including all of the limitations of the base claim and any intervening claims to overcome the objections to being dependent upon a rejected base claim.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

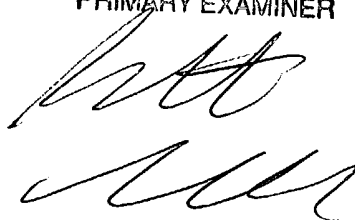
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may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.

May 30, 2004

BENNETT CELSA
PRIMARY EXAMINER

Handwritten signature of Bennett Celsa, Primary Examiner, in cursive script.